

Viral Hemorrhagic Fevers

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Viral Hemorrhagic Fevers

- Fever, myalgia, headache, prostration
- Hemorrhage
- Capillary leak
- Hypotension, shock, death

Hemorrhagic Fever

An acute febrile illness characterized by malaise, myalgia, and prostration dominated by generalized abnormalities of vascular permeability, and regulation. Bleeding manifestations often occur, particularly in severe cases; they are usually diffuse and reflect widespread vascular damage rather than life-threatening volume loss.

Hemorrhagic Fever Viruses: Taxonomy

- Four families of lipid-enveloped viruses with single-stranded RNA genomes
 - Arenaviruses
 - Bunyaviruses
 - Filoviruses
 - Flaviviruses

Hemorrhagic Fever Virus Families

Arenaviridae

- **New World Complex**
 - Argentine HF • Junin Virus
 - Bolivian HF • Machupo Virus
 - Venezuelan HF • Guanarito Virus
 - Brazilian HF • Sabia Virus
- **Old World Complex**
 - Lassa Fever • Lassa Virus

Hemorrhagic Fever Virus Families

Bunyaviridae

- **Phlebovirus Genus**
 - Rift Valley Fever • RVF Virus
- **Nairovirus Genus**
 - Crimean-Congo HF • CCHF Virus
- **Hantavirus Genus**
 - HFRS
 - Korean or Epidemic HF • Hantaan
 - E. Europe • Dobrava-Belgrade
 - Nephropathia Epidemica • Puumala Virus
 - Rat-borne • Seoul

Hemorrhagic Fever Virus Families

Filoviridae

- Ebola HF - Ebola Virus
- Marburg HF - Marburg Virus

Flaviviridae

- **Mosquito-Borne:**
 - Yellow Fever - YF Virus
 - Dengue HF - Dengue Viruses
- **Tick-Borne:**
 - Kyasanur Forest Disease - KFD Virus
 - Omsk HF - OHF Virus

Hemorrhagic Fever Viruses: Ecology

• Maintained in animal reservoirs

- **Arenaviruses:** Rodents
- **Bunyaviruses:**
 - ◊ CCHF: Hares, birds, ticks
 - ◊ Rift Valley: Mosquitoes
 - ◊ Hantaviruses: Rodents
- **Filoviruses:** Unknown
- **Flaviviruses**
 - ◊ Dengue: Monkeys, humans, mosquitos
 - ◊ Yellow fever: Monkeys, mosquitoes

Transmission to Humans

- **Aerosols**
 - Desiccated rodent excreta: Arenaviruses, hantaviruses
 - Generated by field mice caught in agricultural machinery: New World arenaviruses
 - Generated during slaughter of infected livestock: CCHF, RVF
- **Contaminated food/water**
Arenavirus (Lassa)

Transmission to Humans

- **Arthropod vectors:**
 - Mosquitoes
 - ◊ Bunyavirus: RVF
 - ◊ Flaviviruses: Dengue, Yellow fever
 - Ticks
 - ◊ Bunyavirus: CCHF
 - ◊ Flaviviruses: Kyasanur Forest Disease, Omsk HF
 - Hematophagous flies:
 - ◊ Bunyaviruses: RVF

Transmission to Humans: BW Implications

- With exception of dengue, all VHF agents transmitted by aerosol in laboratory (animal models)
- Stabilization in aerosols

Are Viral Hemorrhagic Fevers Important Health Problems?

- **Global interest in VHFs:** Most of world population at risk
- **Argentine HF** 100-1000's of cases disruptive to agriculture
- **Lassa fever** up to 20% of febrile admissions in some W. Africa hospitals
- **Rift Valley fever** broad distribution in Africa; epidemics in 1977, 1993-4, 1998
- **Congo-Crimean HF** broad geographic distribution epidemics and nosocomial outbreaks

Are Viral Hemorrhagic Fevers Important Health Problems? (cont.)

- **HFRS**
 - Annual epidemics in Asia and elsewhere
 - Broad geographic distribution
 - Up to 200,000 cases annually, with half occurring in China
 - Cases among US troops in Korea and Bosnia
 - Seoul virus infects urban rats in USA
 - 3 cases HFRS due to Seoul virus identified in Baltimore

◊ Glass et al. J Infect Dis 1993;167:614-20
 ◊ Glass et al. Nephron 1994;68:48-51

Are Viral Hemorrhagic Fevers Important Health Problems? (cont.)

- **Dengue HF**
 - Endemic in Asia, Indonesia
 - Epidemics in Central America and Caribbean due to expanding range of *Aedes aegypti*
 - Domestically acquired cases- Over 1 million cases and 100,000 deaths annually due to dengue HF
 - Texas, Florida
- **Yellow fever**
 - Annual sylvatic epidemics
 - Potential for urban epidemics
 - High mortality rate among unvaccinated
 - Limited vaccine production
 - potential world-wide

Military Relevance: Endemic/Epidemic VHF

- International Deployments
- Risk of Importation/Exportation of Disease
- Impact on Training and Mobilization
- Impact on Medical Readiness

Military Relevance: Biological Warfare Threats

- **Pro:**
 - Highly infectious by aerosol
 - ◊ Stabilizers to enhance viability
 - High morbidity/mortality
 - Replicate well in cell culture
- **Con:**
 - Lack of vaccine/Rx to protect user

Viral Pathogenesis

- Complex, incompletely understood, varies with specific viruses
- Activation of complement/cytokine cascades
- Activation of coagulation cascades
- Role of organ system failures
 - Yellow Fever: Hepatic failure, deficiency of Vitamin K dependent clotting factors
 - HFRS: Uremia, platelet dysfunction
- Key event: Damage to vascular endothelium

Typical VHF Patient

- **History**
 - Foreign travel to endemic or epidemic area
 - Rural environs (except dengue, urban YF)
 - Nosocomial exposure
 - Contact with arthropod or rodent reservoir
 - Domestic animal blood exposure (CCHF, RVF)
- **Incubation**
 - Typical 5-10 days
 - Range 2-16 days (except Hantavirus: 9-35 days)

Typical VHF Patient

- **Symptoms**
 - Fever, headache, malaise, dizziness
 - Myalgias
 - Nausea/vomiting
- **Initial Signs**
 - Flushing, conjunctival injection
 - Periorbital edema
 - Petechiae
 - Positive tourniquet test
 - Hypotension

VHF Evolution

- Prostration
- Pharyngeal, chest or abdominal pain
- Mucous membrane bleeding, ecchymosis
- Shock
- Usually improving or moribund within a week (except HFRS, arenaviruses)
- Bleeding, CNS involvement, marked elevation SGOT portend poor prognosis
- Mortality agent dependent (<10-90%)

VHF Sequelae

- Prolonged Convalescence
- Hair Loss, Furrowed Nails
- Deafness (Lassa, EBO)
- Retinitis (RVF, KFD)
- Uveitis (RVF, MBG)
- Encephalitis (AHF, BHF, RVF, KFD, OHF)
- Pericarditis (Lassa)
- Renal insufficiency (HFRS)

VHF Clinical Lab

- Leukopenia is suggestive, but WBC may be normal, elevated, or leukemoid
- Thrombocytopenia is typical, but sometimes mild or absent
- Hematocrit normal or increased early
- AST (SGOT) typically elevated; prognostic value
- BUN/Cr related to circulatory status (except in HFRS)

VHF Clinical Lab (cont.)

- Bilirubin, amylase may be elevated
- Prothrombin/APTT usually prolonged
- FSP normal or modestly elevated
- Fibrinogen elevated, normal, or decreased
- Proteinuria usual

VHF: Differential Diagnosis

- **Bacterial**
 - typhoid fever, meningococcemia, rickettsioses, leptospirosis
- **Protozoal**
 - falciparum malaria
- **Other**
 - vasculitis, TTP, HUS, heat stroke

Diagnosis of Zoonotic Viruses

- Epidemiology critical
- Clinical impressions valuable but often ambiguous
- Exclude life-threatening items in DDX:
 - Bacterial sepsis: blood cultures
 - Malaria: thick and thin blood smears (Giemsa stain)
- Laboratory Confirmation:
- Rapid ELISA techniques most easily employed
 - viral antigen detection sensitive to $\sim 10^4$ log PFU/ml
 - IgM antibody capture
- Serology on paired sera may be definitive or highly suggestive

Laboratory Confirmation (Cont'd)

- Nucleic acid hybridization & immunohistochemistry (IHC) of formalin-fixed tissues; Electron microscopy
 - can provide definitive evidence
- Virus isolation from acute blood or necropsy best
- Polymerase chain reaction (PCR)
 - increasingly important tool; undergoing further development

Processing Clinical Specimens

- isolation of virus (Biosafety Level 4)
 - whole blood (w/ anticoagulant)
 - urine, throat swab or wash
 - ◊ in sealed plastic tube w/10% FBS or 1%HSA final conc.
- label each specimen swab exterior of each container with disinfectant
- double-bag, swab exterior with disinfectant *before* removal from patient's room

VHF Management: Cardiovascular

- Hemodynamic resuscitation & monitoring
 - invasive (S-G catheter) as warranted and feasible
- Careful fluid management
 - use of colloid
 - hemodialysis or hemofiltration as needed
 - ◊ esp. HFRS patients
- Vasopressors and cardiotonic drugs
- Cautious sedation and analgesia

VHF Management Hematologic

- DIC may be important in some VHFs (RVF, CCHF, Filoviruses)
- Coagulation studies and clinical judgement as guide
 - replacement of clotting factors
 - platelet transfusions
- No antiplatelet drugs or IM injections

VHF Management Anti-viral Therapy

- Ribavirin
 - *Arenaviridae* (Lassa, AHF, BHF)
 - *Bunyaviridae* (HFRS, RVF, CCHF)
- Immune (convalescent) plasma
 - *Arenaviridae* (AHF, BHF, ?Lassa)
 - Passive immunoprophylaxis post-exposure?

Lassa Fever & CCHF Management Ribavirin

- **Treatment**
 - 30 mg/kg IV single loading dose
 - 16 mg/kg IV q 6 hr for 4 days
 - 8 mg/kg IV q 8hr for 6 days
- **Prophylaxis**
 - 500 mg PO q 6 hr for 7 days

Note: Parenteral and oral ribavirin are investigational and available through human use protocols only

McCormick JB et al. *N Eng J Med* 314(1):20-26, 1986.
Jahriling PB et al. *J Infect Dis* 141:580-589, 1980.

HFRS Therapy Ribavirin

- fever of ≤ 6 days
- intravenous ribavirin treatment regimen:
 - 33 mg/kg (2.0 gm/60kg) single loading dose
 - 16 mg/kg (1.0 gm/60kg) q 6h for 4 days
 - 8 mg/kg (0.5 gm/60kg) q 8h for 3 days

Note: parenteral ribavirin is investigational and available through human use protocol only

Huggins et al. *J Infect Dis* 164:1119-27, 1991.

VHF Management Other

- R/O or treat empirically for malaria, typhoid fever, rickettsioses, etc.
- vigilance against secondary bacterial infections
 - nosocomial pneumonia, UTI, bacteremia

ONLY INTENSIVE CARE WILL SALVAGE THE
SICKEST PATIENTS

Infection Control (Arenavirus, Filovirus, CCHF)

- **Single room w/ adjoining anteroom as only entrance**
 - Handwashing facility with decontamination solution
 - ◊ 0.5% sodium hypochlorite, 2% glutaraldehyde, phenolic detergent, soap
 - ◊ Changing area/protective equipment
- **Negative air pressure; air not recirculated**
 - Prominent hemorrhage, cough, vomiting, diarrhea
 - Consider negative air flow room, if available, in absense of these sxs/sxs to avoid having to transfer pt later

CDC. Update: Management of patients with suspected viral hemorrhagic fever. *MMWR* 44 (No. 25):475-479, June 30, 1995.

CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

Infection Control (Arenavirus, Filovirus, CCHF) (Cont'd)

- **Strict barrier precautions**
 - gloves, gown, mask, shoe covers, protective eyewear/faceshield
- **HEPA-filtered mask or respirator**
 - Prominent hemorrhage, cough, vomiting, diarrhea

CDC. Update: Management of patients with suspected viral hemorrhagic fever. *MMWR* 44 (No. 25):475-479, June 30, 1995.

CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

Infection Control Arenavirus, Filovirus, CCHF (cont.)

- Chemical toilet
- All body fluids disinfected
- Disposable equipment & sharps into rigid containers containing disinfectant -> autoclaved or incinerated
- Double-bag refuse
 - outside bag disinfected then autoclaved or incinerated

CDC. Update: Management of patients with suspected viral hemorrhagic fever. *MMWR* 44 (No. 25):475-479, June 30, 1995.

CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

VHF Management Protection of Medical Personnel

- **Patient care limited to minimal # of caregivers**
 - *reliable and competent-minimize exposure risk*
- **Education**
 - barrier nursing practices, exercise of due care
 - consult AIT, USAMRIID

DO NOT PANIC

High Level Containment Disadvantages

- systems hinder patient care
- *increase possibility of parenteral exposure*
- **personnel must be trained to safely and effectively function**
- **require similar BL-4 laboratory support**
- **expensive**
- **1^o & 2^o medical care personnel must deal w/ suspected VHF patient before such specialized help is available**

Clinical Laboratory Procedures

- **Strict barrier precautions**
 - gloves, gown, mask, shoe covers, protective eye/faceshield
 - consider respirator with HEPA filter
 - handle specimens in biosafety cabinet when possible
- **Spills/splashes**
 - immediately cover with disinfectant, allow to soak for 30'
 - wipe with absorbent towel soaked in disinfectant
- **Waste disposal**
 - same as for patient isolation practices

CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

Exposures First Aid

- **Wash/irrigate wound/site *immediately***
 - within 5 minutes of exposure
- **Mucous membrane (eye, mouth, nose)**
 - continuous irrigation with rapidly flowing water or sterile saline for ≥ 15 minutes
- **Skin**
 - scrub for at least 15' minutes while copiously soaking the wound with soap or detergent solution
 - ◊ fresh Dakin's solution (0.5% hypochlorite): dilute 1 part standard laundry bleach (5% hypochlorite) with 9 parts tap water

Exposures: Surveillance

- **Casual contacts**
 - remote contact with index patient (e.g., same airplane)
 - no known risk
- **Close contacts**
 - household, physical, nursing care, handling lab specimen
 - record temp b.i.d. for 3 weeks post-exposure
 - post-exposure prophylaxis measures warranted if develop fever ($T \geq 101^\circ\text{F}$) or other systemic symptoms within 3 weeks post-exposure

CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

Post-Exposure Prophylaxis

- **High-risk contacts**
 - mucous membrane (e.g., kissing, sexual intercourse); needlestick or other penetrating injury involving exposure to patient's secretions, excretions, blood, tissues, or other body fluids
 - post-exposure prophylaxis measures warranted if available

VHF Vaccines

- **YELLOW FEVER**
 - licensed 17D vaccine safe and efficacious
 - cannot be used in persons with egg allergy
- **ARGENTINE HEMORRHAGIC FEVER**
 - live, attenuated
 - safe and efficacious; used in 150,000
 - protects monkeys against Bolivian HF

VHF Vaccines

- **RIFT VALLEY FEVER**
 - formalin-inactivated
 - ◊ safe but requires 3 shots, intermittent booster
 - ◊ limited supply
 - live, attenuated MP-12
 - ◊ Phase II testing
- **HFRS (HANTAAN)**
 - vaccinia vectored recombinant vaccine

Aeromedical Isolation Team

- **High-level protection against small-particle aerosol infection**
 - Plastic isolator for transport stretcher
 - ◊ negative pressure with HEPA exhaust
 - Positive pressure suits for medical personnel
- **Medical consultation**
 - contact USAMRIID and ask for MOD on call
 - ◊ DSN 343-2257, (301) 619-2257
 - Transport arrangements
 - ◊ Maj Nerges: DSN 343-4647; sky pager (800) 901-6233
 - ◊ can transport 1-2 patients

Viral Hemorrhagic Fevers

Disease	Geography	Source of Human Infection ^a	Incubation (days)
Lassa	Africa	Rodent (Nosocomial)	5-16
AHF/BHF	South America	Rodent	7-14
RVF	Africa	Mosquito (Slaughter)	2-5
CCHF	Europe, Asia, Africa	Tick (Slaughter of domestic animal)	3-12
HFRS	possibly world-wide	Rodent	9-35
Marburg/Ebola	Africa	Unknown (Nosocomial)	3-16
Yellow Fever	Tropical Africa, South America	Mosquito	3-15
Dengue HF	Asia, Americas, Africa	Mosquito	3-15
KFD/OMSK	Mysore, India/Russia	Tick (Muskrat-contaminated water)	3-8

^aUsual source in nature (other routes in parentheses).

Viral Hemorrhagic Fevers

Taxon	Disease	Clinical	Pathogenesis
Arenaviridae	Lassa fever	Hemorrhage & neurologic involvement seen in severe cases; deafness; pericarditis may occur during recovery	High AST and viremia predict fatal outcome
	Argentine & Bolivian HF	Prominent neurologic manifestations; petechiae and hemorrhage common	Bone marrow and CNS infection
Bunyaviridae	Phlebovirus	retinitis; hemorrhage and hepatitis with icterus occur infrequently	DIC in monkey model
	Nairovirus	copious hemorrhage & extensive ecchymoses may dominate clinical picture more prominently than with other HF	
	Hantavirus	Hemorrhagic fever with renal syndrome	Renal involvement prominent; intrinsic disease feature; long incubation period

Viral Hemorrhagic Fever

Disease	Maintenance	Amplification	Infection of man	Human to Human
Lassa	Rodent: <i>Mastomys natalensis</i>		Aerosol, fomites	Contact Nosocomial (occasional)
Argentine HF	Rodent: <i>Calomys musculus</i>	Other rodents?	Aerosol, fomites	Venereal (occasional) Nosocomial (rare)
Bolivian HF	Rodent: <i>Calomys callosus</i>		Aerosol, fomites	Venereal (suspected) Nosocomial (rare)
Rift Valley fever	Mosquito: flood water <i>Aedes</i>	Sheep & cattle with other mosquitoes	Mosquito bite (biological transmission, interrupted feeding) Aerosol or fomites from slaughter of domestic animals	needlestick

Viral Hemorrhagic Fever (cont.)

Disease	Maintenance	Amplification	Infection of man	Human to Human
Congo-Crimean HF	Ticks: principally <i>Hyalomma</i>	Intermediate tick hosts	Tick bite, Crushing tick; slaughter or milking of infected animal. Fomite or aerosol (occasional)	Nosocomial (occasional)
HFRS	Rodents: several genera of Muridae superfamily		Aerosol, possibly fomites	None
Marburg Ebola	Unknown		Unknown	Contact Nosocomial
Yellow fever	Sylvan Mosquito-primate cycle; <i>Aedes</i> in Africa and <i>Haemagogus</i> in Americas principally Transovarial in mosquitoes and ticks rarely	Primates	Mosquito bite	needlestick

Viral Hemorrhagic Fevers (cont.)

Taxon	Disease	Clinical	Pathogenesis
Filoviridae	Marburg disease, Ebola HF	Extreme prostration, cachexia, maculopapular rash, abdominal pain, diarrhea common; high (>50%) mortality	DIC implicated
Flaviviridae	Mosquito Yellow fever	Black vomit; jaundice with midzonal liver necrosis	B-cell necrosis; terminal hepatorenal syndrome?
	Dengue HF	Maculopapular rash, arthralgias, vascular permeability with petechiae, edema, and hemorrhage	Antibody enhancement of macrophage infection; complement activation
Tick	Kyasanur Forest disease, Omsk HF	Pulmonary involvement; biphasic illness with subsequent CNS disease	

Viruses	Disease	In vitro neutralization by convalescent sera	In vitro Interferon Sensitivity	Ribavirin
Arenaviridae	Lassa fever Argentine & Bolivian HF	+ ++	low low	yes yes
Bunyaviridae	Phlebovirus Rift Valley fever Nairovirus Congo-Crimean HF Hantavirus HFRS, HPS	+++ +? +++	yes yes yes	yes yes yes
Filoviridae	Marburg disease, Ebola HF	0	low	no
Flaviviridae	Mosquito borne Yellow fever Dengue HF	+++ +++	yes yes	low low
	Tick borne Kyasanur Forest disease, Omsk HF	+++	yes	low

Argentine, Bolivian, and Venezuelan Hemorrhagic Fevers

- rodent-borne (aerosol) in South America
 - nosocomial transmission rare
- petechiae & other hemorrhages neurologic manifestations w/ normal CSF
- incubation period 7-14 days
- shock, pulmonary edema, GI hemorrhage, CNS dz (tremors, dysarthria, seizures)
- lab: low wbc, plt, and complement; proteinuria, prerenal
- Dx: Ag detection and IgM capture ELISA virus isolation (serum, buffy coat, semen)

Lassa Fever

- rodent-borne in West Africa
 - nosocomial: exposure to body fluids
- pharyngitis with exudate, hypotension, cough, abd pain, edema and effusions, lymphadenopathy
 - hemorrhage not common except in severe cases
 - deafness, pericardial friction rub during recovery
- incubation period 5-16 days
- elevated AST, CPK, and amylase; proteinuria; mildly low or normal wbc and plt
- Dx: Ag detection and IgM capture ELISA virus isolation from serum, urine, throat

Congo-Crimean Hemorrhagic Fever

- tick-borne in Africa, Asia, E. Europe, Middle East
 - nosocomial via body fluid exposure (?aerosol)
- extensive hemorrhage and ecchymoses, hypotension, hepatomegaly, abdominal pain, jaundice, toxicity
- incubation period 3-12 days
- Low plt & fibrinogen, elevated PT/PTT & FSP, lymphopenia, elevated LFT's and bili
- Dx : Ag detection and IgM capture ELISA virus isolation (serum)

Rift Valley Fever

- mosquito-borne in sub-Saharan Africa
 - nosocomial infection not reported but aerosol transmission possible
- fever, headache, myalgias, retinitis
 - infrequently complicated by hemorrhage, severe hepatitis with jaundice, and/or encephalitis
- incubation period 2-5 days
- low wbc and plt, transaminitis with elevated bili and alk phos, prolonged PT/PTT
- Dx : Ag detection and IgM capture ELISA
virus isolation (serum)

Hemorrhagic Fever with Renal Syndrome

- rodent-borne (aerosol)
 - HFRS: Asia (Hantaan, Seoul), Europe (Hantaan, Dobrava), USA (Seoul)
 - nephropathia epidemica in Europe (Puumala)
 - May complicate HPS due to Bayou, Black Creek Canal, and South American hantaviruses
- fever, shock, hemorrhage, renal failure
- incubation period 9-35 days
- low plt, renal azotemia
- Dx : IgM capture ELISA

Ebola and Marburg

- unknown reservoir in Central and East Africa
 - nosocomial: transmission usu. via exposure to body fluids, but possible by fomite or droplet
- severe prostration with delirium, maculopapular rash, DIC
 - abdominal pain, petechiae, GI hemorrhage, hepatitis, edema, prerenal azotemia, shock
- incubation period 3-16 days
- low wbc, plt; positive FSP; transaminitis; proteinuria, azotemia
- Dx: virus isolation from serum, urine, semen, throat or rectal swab

Yellow Fever

- mosquito-borne in tropical Americas and sub-Saharan Africa
- jaundice, midzonal liver necrosis, black vomit, relative bradycardia
- incubation period 3-15 days
- low wbc and plt, proteinuria, elevated SGOT, prolonged PT/PTT
- Dx : IgM capture ELISA
virus isolation (serum)

Dengue Hemorrhagic Fever

- mosquito-borne in tropical Americas, Africa, Asia
- maculopapular rash sparing palms and soles, arthralgias, capillary friability
 - positive tourniquet test, petechiae and mucosal hemorrhage, shock
- incubation period 3-15 days
- low plt and fibrinogen, lymphocytosis, hemoconcentration, depressed C3 and C4
- Dx : IgM capture ELISA
virus isolation (serum, buffy coat)

Pathogenesis: Dengue Hemorrhagic Fever

- Four different serotypes of Dengue virus
- Initial infection: Neutralizing Ab vs. initial strain
- Re-infection due to different serotype: Non-neutralizing Ab
 - Immune complexes c live virus
 - Enhanced uptake by monocytes
 - Infection/lysis of monocytes-release of cytokines, anticoagulants, procoagulants
- Implications re vaccine development

Kyasanur Forest Disease Omsk Hemorrhagic Fever

- **tick-borne in India (KFD) and Siberia (Omsk)**
 - nosocomial transmission not reported
- **systemic toxicity, pulmonary infiltrates biphasic course with later CNS involvement**
 - becomes afebrile, then develops neurologic disease
- **incubation period 3-8 days**
- **low wbc and plt**
- **Dx: IgM capture ELISA**